Risk of Parkinson Disease Onset in Patients With Diabetes

A 9-year population-based cohort study with age and sex stratifications

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OBJECTIVE—We retrospectively assessed the age- and sex-specific incidence and relative risk of Parkinson disease (PD) in Taiwan's diabetic population.

RESEARCH DESIGN AND METHODS—Study cohort included 603,416 diabetic patients and 472,188 nondiabetic control subjects. Incidence rate and relative risk of PD (ICD-9-CM 332.0) were evaluated.

RESULTS—The incidence of PD was 3.59 and 2.15 per 10,000 person-years for the diabetic and control group, respectively, representing a covariate adjusted hazard ratio (HR) of 1.61 (95% CI 1.56–1.66), which was substantially reduced to 1.37 (1.32–1.41) after adjusting for medical visits. Diabetes was associated with a significantly elevated risk of PD in all sex and age stratifications except in young women, with the highest HR noted for young men aged 21–40 years (2.10 [1.01–4.42]), followed by women aged 41–60 (2.05 [1.82–2.30]) and >60 years (1.65 [1.58–1.73]).

CONCLUSIONS—Diabetes is associated with an increased risk of PD onset in a Chinese population, and the relation is stronger in women and younger patients.

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A few recent studies raise the possibility of increased risk of Parkinson disease (PD) among diabetic patients (1–3). However, findings reported in prior studies are not consistent (4–7). Furthermore, large-scale population-based cohort studies with detailed age and sex stratifications in Asia are rare. The current study uses a national cohort retrieved from Taiwan's National Health Insurance (NHI) database to retrospectively investigate the age- and sex-specific associations of diabetes with the risk of incident PD.

RESEARCH DESIGN AND METHODS

—Details of NHI claim data of Taiwan and methods of selection of diabetic and control groups were described previously (8,9). In brief, eligible study subjects were adult prevalent cases of diabetes with a diagnosis of diabetes (ICD-9 250 or A code 181) in 2000 (i.e., index date) who then experienced one or more diabetes diagnoses within the subsequent 12-month follow-up period. The first and last outpatient visits within 1 year had to be >30 days apart to avoid accidental inclusion of miscoded patients. The index date for subjects in the control group was the first date of enrollment to NHI. If their first date of enrollment was before 1 January 2000, the index date was set as 1 January 2000. The original study subjects consisted of 615,532 diabetic patients and 614,871 age- and sex-matched control subjects randomly selected from the registry of beneficiaries (8,9). Case subjects with a prior diagnosis of PD (ICD-9 332.xx, n = 2,977) or secondary Parkinsonism (n = 3,639) from 1 January 1997 to the index date were excluded. Case subjects aged <20 years were also excluded (n = 5,500). The same exclusion criteria were also applied to control subjects (PD, n = 1,699; secondary Parkinsonism, n = 1,398; age <20, n = 5,497). Control subjects treated for diabetes (ICD-9: 250.xx) during follow-up (i.e., 2000–2008) (n = 134,089) also were excluded to reduce the likelihood of disease misclassification. The final cohort consisted of 603,416 diabetic patients and 472,188 control subjects.

We identified the first diagnoses of PD (ICD-9: 332.0) from outpatient claims or hospitalization records from 2000 to 2008 as the study end point. Only those with end point onset 1 year after the index date were retrieved to establish the temporal link between diabetes and PD. All of the study subjects were followed from the index date to occurrence of end point, withdrawal from the NHI, or 31 December 2008, whichever date came first, and the later two dates were considered as censoring observations.

The age- and sex-specific incidence densities (IDs) were determined under Poisson assumption. Cox proportional hazards regression models were performed with adjustment for age, sex, geographic area, urbanization status, and comorbidities, including hypertension (ICD-9: 401–405), hyperlipidemia (ICD-9: 272), and cardiovascular disease (ICD-9: 410–414, 430–438). We also tested the interactive effects of diabetes with age or sex on risk of PD. We adjusted for geographic area to minimize the potential confounding by

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differential accessibility and availability of medical care (10). Adjustment for urbanization was to account for the possible urban-rural difference in prevalence of certain environmental factors, such as well-water drinking, herbicides, pesticide exposure, and neurotoxins, which have been considered as risk factors for PD (11). All statistical analyses were performed with SAS (version 9.2; SAS Institute, Cary, NC). A statistical significance was declared at a type I error of 0.05.

RESULTS—The overall ID for diabetic men and women was 3.34 and 3.82 per 10,000 patient-years, respectively, while the corresponding figures for control men and women were 2.12 and 2.18 per 10,000 patient-years. Irrespective of sex, the ID increased with age in both groups, with a dramatically high ID noted for those aged >65 years (Table 1).

Compared with control subjects, diabetic patients showed a significantly increased risk of PD with an adjusted hazard ratio (HR) of 1.61 (95% CI 1.56–1.66). The adjusted HR was significantly higher ($\beta = 0.109657$, $P < 0.0001$) in diabetic women (1.70 [1.63–1.77]) than in diabetic men (1.51 [1.44–1.57]). The interaction of diabetes with age was also statistically significant for both men ($\beta = 0.18082$, $P = 0.0014$) and women ($\beta = 0.30550$, $P < 0.001$). For men, the age-specific HR was highest in young diabetic subjects aged 21–40 years (2.10), then it declined to 1.60 and 1.49 for aged 41–60 and >60 years, respectively. The age-specific HR was lower for young women with diabetes (1.10) and was higher for middle-aged and older women with diabetes (2.05 and 1.65, respectively) (Table 1). To test the proportionality assumption of the Cox model, we performed stratified analysis according to the period of follow-up. The adjusted HR tended to be higher in earlier years (i.e., 2000–2004; 1.83 [1.75–1.91]) than in later years (i.e., 2005–2008; 1.44 [1.39–1.50]). We also calculated the HR for diabetic subjects whose dates of first-time ambulatory visit for diabetes were in 1997 or earlier, 1998–1999, or 2000 and observed an adjusted HR of 1.72 (1.66–1.77), 1.38 (1.32–1.44), and 1.25 (1.18–1.33), respectively.

To examine the potential bias arising from higher ambulatory care frequency in diabetic patients, we limited control subjects to those with ≥21 ambulatory visits (the average number of ambulatory visits for nondiabetic causes in diabetes) for all causes in 2000 and noted an overall adjusted HR of 1.37 (1.32–1.41).

CONCLUSIONS—This retrospective study supports the putative link between diabetes and risk of PD (1–3). Our study provides additional information suggesting significant effect modifications by age and sex. We found a significantly higher HR of PD in diabetic women than in diabetic men. Moreover, young diabetic men aged 21–40 years or diabetic women aged 41–60 years are more vulnerable to the increased risk.

The association between diabetes and PD has not been fully illustrated. It is possible that chronic inflammation and oxidative stress noted in diabetes may also lead to higher risk of PD years later (3). Besides, animal and in vitro studies show a role for insulin in the regulation of brain dopaminergic activity. Insulin dysregulation and changes in insulin action have been of concern in the pathophysiology and clinical symptoms of PD (12). Furthermore, reduced expression of certain genes in type 2 diabetes is related to impaired mitochondrial oxidative pathway, while mitochondrial dysfunction has been suggested as a pathogenesis in PD (2,13). Our finding indicates a stronger association of diabetes with early onset PD (age <60 years), which is consistent with one recent study (2).

The limitation of this study is that we could not differentiate between type 1 and type 2 diabetes, despite the fact that type 1 diabetes constitutes only 1.8% of all diabetes in Taiwan (14). We limited the diabetic patients to those diagnosed after age 20 or older to further minimize this problem. In addition, because of a lack of complete information on subjects' lifestyle and environmental or occupational exposure, our study was unable to directly adjust for the potential confounding of those variables. The HR in diabetes was substantially decreased from 1.61 to 1.37 after adjusting for frequency of ambulatory care, suggesting major confounding by medical attention, which also may explain some of the remaining risk elevation.

During a 9-year study period, the diabetic patients in Taiwan experienced significantly increased risks of PD in both sexes and most ages; a stronger link between diabetes and young-onset PD deserves further investigation.

Table 1—*Overall and age- and sex-specific IDs and relative hazards of PD in the diabetic and control groups*

	Control group			Diabetic group				
Variable*	Subject (*n*)	Event (*n*)	ID (95% CI) per 10,000 patient-years‡	Subject (*n*)	Event (*n*)	ID (95% CI) per 10,000 patient-years‡	HR (95% CI) in association with diabetes	Adjusted HR§ (95% CI) in association with diabetes
Men								
Age (years)								
21–40	20,660	2	0.09 (0.05–0.14)	21,310	4	0.22 (0.16–0.30)	2.57 (1.42–4.67)	2.10 (1.01–4.42)
41–60	102,883	47	0.55 (0.50–0.60)	128,217	108	1.06 (0.99–1.12)	1.96 (1.76–2.18)	1.60 (1.41–1.81)
>60	109,636	338	4.29 (4.15–4.44)	140,593	599	6.41 (6.25–6.58)	1.52 (1.46–1.59)	1.49 (1.42–1.56)
Total	233,179	387	2.12 (2.06–2.19)	290,120	711	3.34 (3.26–3.42)	1.59 (1.53–1.65)	1.51 (1.44–1.57)
Women								
Age (years)								
21–40	14,718	2	0.11 (0.06–0.19)	14,881	3	0.22 (0.15–0.32)	2.00 (1.05–3.79)	1.10 (0.48–2.55)
41–60	97,508	52	0.62 (0.56–0.67)	125,561	156	1.51 (1.44–1.59)	2.48 (2.25–2.74)	2.05 (1.82–2.30)
>60	126,783	368	3.80 (3.67–3.92)	172,210	743	6.18 (6.04–6.32)	1.66 (1.59–1.72)	1.65 (1.58–1.73)
Total	239,009	422	2.18 (2.11–2.24)	312,652	902	3.82 (3.74–3.90)	1.77 (1.71–1.84)	1.70 (1.63–1.77)
Overall	472,188	809	2.15 (2.10–2.20)	603,416	1,613	3.59 (3.53–3.64)	1.69 (1.64–1.73)	1.61 (1.56–1.66)

*Inconsistency between total population and population summed for individual variable was the result of missing information. ‡Based on Poisson assumption. §Based on Cox proportional hazards regression with adjustment for age, sex, geographic area, urbanization status, hypertension, hyperlipidemia, and cardiovascular disease.

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Y.S. researched data and wrote the manuscript. Y.-H.C. analyzed data and drafted the results. H.-F.C. managed data, contributed to discussion, and reviewed and edited the manuscript. Y.-H.S. and H.-F.S. contributed to discussion and drafted the conclusion. C.-Y.L., the principal investigator, researched data and reviewed and edited the manuscript. C.-Y.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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